By
Assist Prof.
Dr. Amin Tur

L.3:Minimal Change Nephrotic Syndrome

It is idiopathic nephrotic syndrome which is more common in boys than in girls (2 : 1) and most commonly appears between the ages of 2 and 6 yr, but, it has been reported as early as 6 mo of age and throughout adulthood.
MCNS is present in 85-90% of patients <6 yr of age and only in 20-30% of adolescents.

Clinical features:

1. The initial episode and subsequent relapses of idiopathic nephrotic syndrome usually preceded by minor infections (commonly URTI) and, uncommonly, reactions to insect bites and beestings.
2. Children usually present with mild edema, which is initially noted around the eyes and in the lower extremities.
   With time, the edema becomes generalized, with the development of ascites, pleural effusions, and genital edema.
3. Anorexia, irritability, abdominal pain, and diarrhea are common.
4. Absence of hypertension and gross hematuria.

A diagnosis other than MCNS should be considered in children <1 yr or > 12 yr of age, with a positive family history of nephrotic syndrome, and/or the presence of extrarenal findings (e.g., arthritis, rash, anemia), hypertension or pulmonary edema, acute or chronic renal insufficiency, and gross hematuria.

Differential diagnosis of marked edema: protein-losing enteropathy, hepatic failure, heart failure, acute or chronic glomerulonephritis, and protein malnutrition.

Investigations:

1. Urinalysis: Shows 3+ or 4+ proteinuria, and microscopic hematuria is present in 20% of children.
2. A spot urine protein : creatinine ratio should be >2.
3. Normal serum creatinine and BUN levels, but they may be elevated if there is decreased renal perfusion due to decrease intravascular volume.
4. The serum albumin level is <2.5 g/dL (Hypoalbuminemia)
5. Increased serum cholesterol and triglyceride levels (Hyperlipidemia).
6. Normal serum complement levels (C3).
7. Renal biopsy is not routinely performed in patient with typical MCNS, but it indicated in:
   a. age <1 yr or >12 yr
   b. gross hematuria,
   c. hypertension.
   d. renal insufficiency.
   e. Hypocomplementemia (low C3 levels)
   f. positive family history of nephrotic syndrome,
   g. presence of extrarenal findings (e.g., arthritis, rash, anemia)
   h. steroid resistance, steroid dependent or frequent relapsing NS.

Treatment MCNS:

A. General considerations:

1. Patients with first episode of NS with mild-moderate edema could be manage as outpatient at home.
2. Child's parents should learn about the signs and symptoms of the disease and its complications, how use the dipstick and interpretations the results for proteinuria.
3. Tuberculosis must be excluded before starting corticosteroid therapy by a purified protein derivative (PPD) skin test.

B. Corticosteroid (CS) therapy:

CS are the mainstay of MCNS therapy. Children with uncomplicated nephrotic syndrome between 1 and 8 yr of age are likely to have steroid-responsive MCNS, and steroid therapy initiated without need of renal biopsy.

Regimen:

Prednisolone as a single daily dose of 60 mg/m2/day or 2 mg/kg/day to a maximum of 60 mg daily for 4-6 wk followed by alternate-day prednisone (starting at 40 mg/m2/d or 1.5 mg/kg/d) for a period ranging from 8 wk to 5 mo, with tapering of the dose. Approximately 80-90% of children respond to steroid therapy.

Response is defined as the achievement of remission within the initial 4 wk of corticosteroid therapy.

Remission consists of a urine protein : creatinine ratio of <0.2 or <1+ protein on urine dipstick for 3 consecutive days. The vast majority of children who respond to prednisone therapy achieve remission within the first 5 wk of treatment.

C. Treatment of Edema:

1. Children with severe symptomatic edema, including large pleural effusions, ascites, or severe genital edema, should be admitted to the hospital.
2. Sodium restriction (<1500 mg daily) and water/fluid restriction may be necessary.
3. A swollen scrotum may be elevated with pillows to enhance fluid removal by gravity.
4. Loop diuretics (furosemide), 1-2 mg/kg/dose orally or intravenously, **should be used with extreme caution** because aggressive diuresis can lead to I.V volume depletion and an increased risk for acute renal failure and I.V thrombosis.
5. In patient with severe generalized edema with evidence of I.V volume depletion (e.g., hemoconcentration, hypotension, tachycardia), IV administration of 25% albumin (0.5-1.0 g albumin/kg) as a slow infusion followed by furosemide (1-2 mg/kg/ dose IV) is indicated.
   Complications of IV albumin therapy: Symptomatic volume overload, hypertension, heart failure, and pulmonary edema.

D. Treatment of Relapse:

Relapse of nephrotic syndrome is defined as a urine protein : creatinine ratio of >2 or ≥3+ protein on urine dipstick testing for 3 consecutive days.

Relapses are common, especially in younger children, and are often triggered by upper respiratory or gastrointestinal infections.

Relapses are usually treated similarly to the initial episode, except that daily prednisone courses are shortened. Daily high-dose prednisone is given until the child has achieved remission (urine protein : creatinine ratio of <0.2 or <1+ protein on urine dipstick for 3 consecutive days), and the regimen is then change to alternate-day therapy.

Steroid Resistance NS: Is defined as the failure to achieve remission after 8 wk of corticosteroid therapy.
Children with steroid-resistant NS require further evaluation, including a diagnostic kidney biopsy, evaluation of kidney function, and quantitation of urine protein excretion (in addition to urine dipstick testing). It usually caused by FSGS (80%), MCNS, or membranoproliferative glomerulonephritis.

Steroid dependent NS: It mean that the patient who responded to daily CS therapy have relapse shortly after switching to or after terminating the alternate-day therapy.

Alternative Therapies to CS in the Treatment of NS:

1. Cyclophosphamide: Its indicated in steroid-dependent patients, frequent relapses, and steroid-resistant patients particularly if they have severe corticosteroid toxicity (cushingoid appearance, hypertension, cataracts, and/ or growth failure). It prolongs the duration of remission and reduces the number of relapses.

The potential *side effects* of the drug (neutropenia, disseminated varicella, hemorrhagic cystitis, alopecia, sterility, increased risk of future malignancy) should be carefully discussed with the family before initiating treatment.

Dose: 2 mg/kg is given as a single oral dose for a total duration of 8-12 wk. Alternate-day prednisone therapy is continued during the course of cyclophosphamide therapy. During cyclophosphamide therapy, the white blood cell count must be monitored weekly and the drug should be stopped if the count falls below 5,000/mm3

2. Calcineurin inhibitors (cyclosporine) is recommended as initial therapy for children with steroid-resistant NS.
Side effects: hypertension, nephrotoxicity, hirsutism, and gingival hyperplasia.

3. Mycophenolate (immunosuppressant drug) can maintain remission in children with steroid-dependent or frequently relapsing nephrotic syndrome.
4. Levamisole, an antihelmintic agent with immunomodulating effects that has been shown to reduce the risk of relapse in comparison to prednisone
5. Angiotensin-converting enzyme inhibitors and **angiotensin II receptor blockers** may be helpful as adjunct therapy to reduce proteinuria in steroid-resistant patients.

Immunizations of nephrotic children:

1. Give full pneumococcal vaccination and influenza vaccination annually to the child and their household contacts
2. Postponed vaccination with live vaccines until the prednisone dose is below either 1 mg/kg daily or 2 mg/kg on alternate days.

3. Live virus vaccines are contraindicated in children receiving corticosteroid sparing agents such as cyclophosphamide or cyclosporine.
4. Following close contact with varicella infection, give patients on immunosuppressive agents varicella-zoster immune globulin **and** immunize healthy household contacts with live vaccines to minimize the risk of transfer of infection to the nephrotic child, but avoid direct exposure of the child to gastrointestinal or respiratory secretions of vaccinated contacts for 3-6 wk after vaccination.

Complications of NS:

1. Infection is a major complication of NS. The common infection is **Spontaneous bacterial peritonitis**, although sepsis, pneumonia, cellulitis, and UTI may be seen.
   Management:
   a. If infection is suspected, a blood culture should be done prior to starting empiric antibiotic therapy.
   b. In the case of spontaneous bacterial peritonitis, peritoneal fluid should be collected and sent for cell count, Gram stain, and culture.
   c. The empirical antibiotic should cover *Pneumococcus* and Gram-negative bacter using 3rd-generation cephalosporin.

2. Increased risk of thromboembolism (Both arterial and venous thrombosis) which ca minimize by avoidance of aggressive use of diuretics and indwelling catheters if possible.
   Anticoagulation therapy is effective including heparin and warfarin

3. Cardiovascular disease e.g. myocardial infarction is a rare complication in childre It is due to hyperlipidemia, particularly in patients with complicated NS

Prognosis:

- Most children with steroid-responsive NS have repeated relapses, which generally decrease in frequency with child age.
- Children who respond rapidly to steroids and those without relapses during the first mo after diagnosis are likely to have infrequently relapsing course.
- It is important to explain to the family that the child with steroid-responsive NS is unlikely to develop chronic kidney disease, the disease is rarely hereditary, and the child (in the absence of prolonged cyclophosphamide therapy) will remain fertile.
- Children with idiopathic NS should not be considered chronically ill and should participate in all age-appropriate childhood activities and maintain an unrestricted die when in remission.
- Children with steroid-resistant NS, most often caused by FSGS, have poorer prognosis. These children develop progressive renal insufficiency, ultimately leading to end stage renal disease requiring dialysis or kidney transplantation. Recurrent nephrotic syndrome develops in 30-50% of transplant recipients with FSGS.